

ÓBUDA UNIVERSITY



DEVELOPMENT OF FUNCTIONALIZED  
CALIX[4]RESORCINARENE-BASED SENSOR PLATFORMS  
FOR HEAVY METALS IONS DETECTION IN AQUEOUS  
SOLUTIONS

THESES BOOKLET

FOR THE DOCTOR OF PHILOSOPHY DEGREE AWARD  
AT THE DOCTORAL SCHOOL OF MATERIALS SCIENCE AND TECHNOLOGIES

BY: LARBI EDDAIF

UNDER THE SUPERVISION OF DR. ABDUL SHABAN

BUDAPEST, 2021

**“Development of Functionalized Calix[4]resorcinarene-Based  
Sensor Platforms for Heavy Metals Ions Detection in Aqueous  
Solutions”**

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## Introduction

### *Statement of the problem*

The recognition of heavy metals ions (HMs) in real samples is a difficult task, the main restrictions are the complexity of their matrices and their very low concentrations, often below the detection limits (LODs) of available techniques. On large scale, myriads of analytical and physicochemical procedures have been used to gather information on HMs determination and monitoring in water sources, these approaches provide very fine and complete information in terms of sensitivity and selectivity, but significant constraints associated with complication and duration of analysis (sampling, preparation, calibration, etc.) are confronted.

The reputation of sensors is well acknowledged, owing to their capability of conducting recognition investigations that were once dominated by analytical chemistry techniques, more advantages are offered by sensors viz. instrumentation low-cost, portability, data acquisition speed, technical reliability, real-time label-free onsite employment, and an overtime mapping-out of the target elements' existence in the studied environment, this later benefit is prohibitively costly when it comes to traditional detection procedures. The design, construction, integration, and real application of HMs chemosensors are comprehensively reported in the literature, upon employing sensing platforms ranging from inorganic and nanomaterials to organic and macrocyclic elements, by way of illustration calixarenes and resorcinarenes. However, the mainstream of Calix-based sensors targeting HMs in water matrices is of either electrochemical concept or optical principle. Yet, to the best of the author's knowledge, no systematic study has been carried out employing techniques as Quartz Crystal Microbalance (QCM) to develop Calix-sensors for such applications.

### *Aims and objectives of the research*

The aims of this research are:

- To perform the synthesis of resorcinarene molecules,
- To characterize the synthesized resorcinarene molecules, using several analytical methods (Fourier Transform Infra-Red spectroscopy (FTIR), X-Ray Diffraction (XRD), Nuclear Magnetic Resonance spectroscopy (NMR), and thermal analyses (TG-DSC-MS)),
- To investigate the complexing abilities of the resorcinarenes' ultra-thin layers utilizing the surface-pressure area isotherms based on the Langmuir technique,
- To investigate the potential applications of the synthesized molecules as recognition elements in detecting HMs, through applying the novel quartz crystal microbalance with impedance capability measurements device (QCM-I) and other electrochemical methods,

namely cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), and square wave voltammetry (SWV).

## Methodology

### *Synthesis and characterization of Calix[4]resorcinarenes*

The synthesis of Calix[4]resorcinarenes was carried out via cyclo-condensation reactions, the confirmation of their chemical structures was performed through FTIR, and  $^1\text{H}/^{13}\text{C}$  NMR. Other properties as the thermal behavior, purity, and crystallinity degree were investigated utilizing TG-DSC-MS, and P-XRD.

### *Langmuir analysis*

To demonstrate the interactions between the metals ions and the ionophores, the Langmuir technique (Specifically the surface pressure-area ( $\Pi$ -A) isotherms) is considered a powerful tool. Accordingly, Langmuir films of resorcinarene molecules were developed at the air/water interface, and the surface pressure against the molecular area variations was recorded.

### *Detection of heavy metals*

The resorcinarene molecules were deposited onto gold surfaces of quartz crystal resonators (QCRs) and screen-printed electrodes (SPEs) to produce functioning detection platforms. The modified QCRs and SPEs sensors were successfully applied by the QCM-I and electrochemical methods as resorcinarene-sensor platforms and effectively detected the presence of HMs at a very low level.

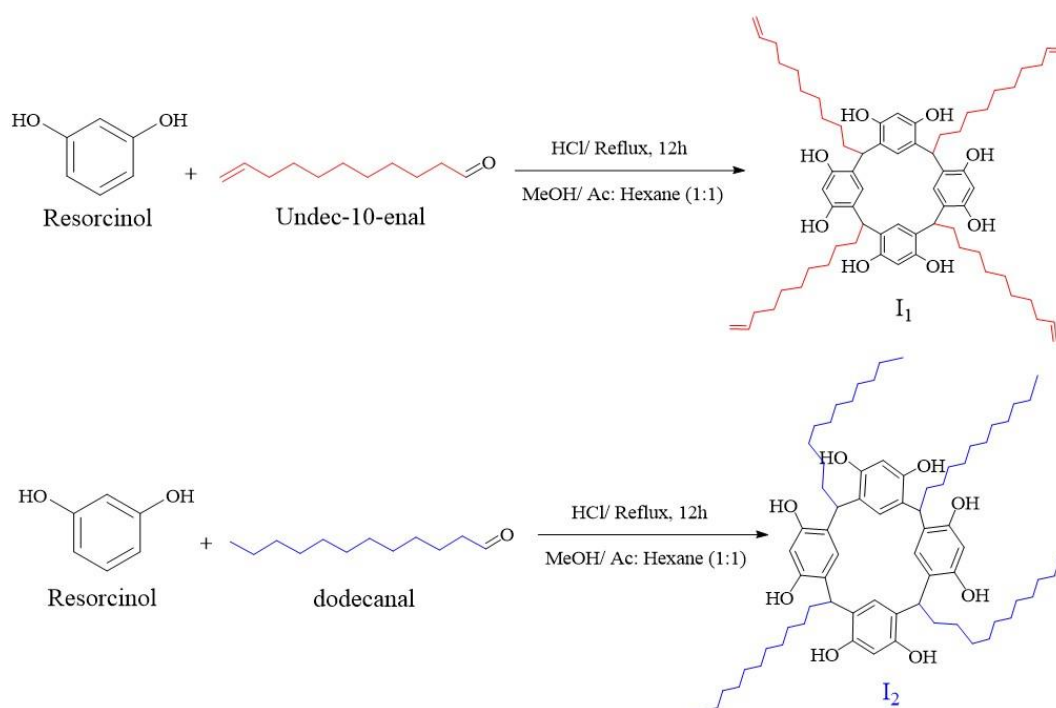
## Main Results

### *Synthesis and characterization of Calix[4]resorcinarenes*

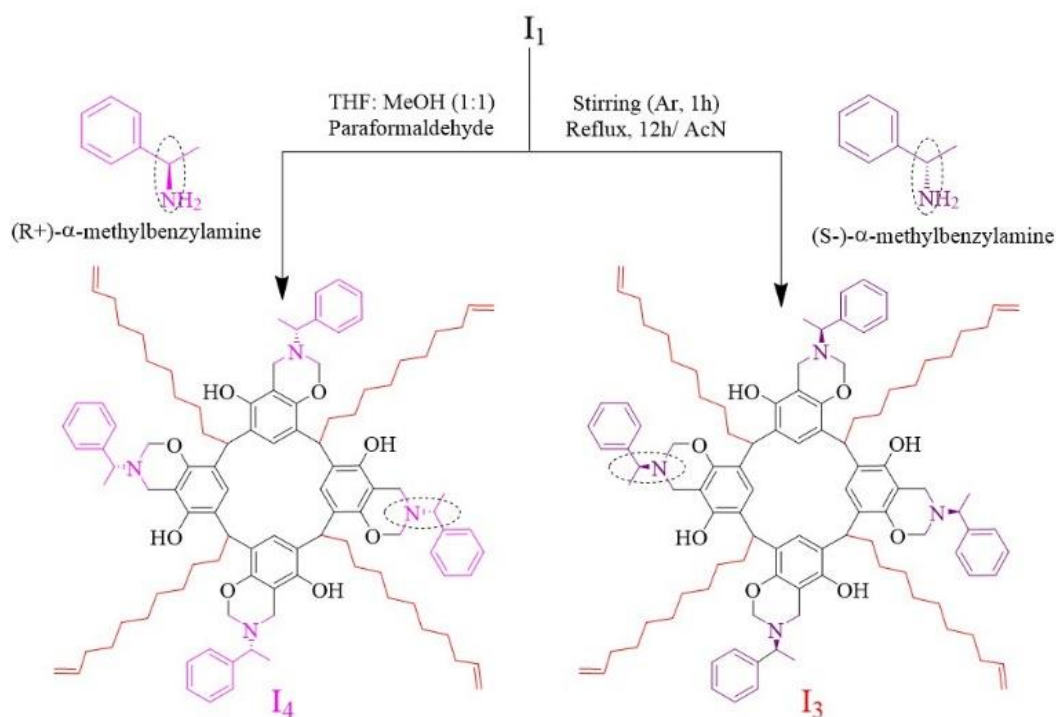
Calix[4]resorcinarenes ( $\text{I}_1$ - $\text{I}_4$ ), comprising two novel enantiomeric ionophores ( $\text{I}_3$ ,  $\text{I}_4$ ) bearing chiral moieties, were produced via acid-catalyzed cyclocondensation reactions (**Figs. 1 and 2**). The functional groups of ( $\text{I}_1$ - $\text{I}_4$ ) were determined via FTIR analyses, their aliphatic and aromatic chemical shifts were established by NMR investigations, the FTIR and NMR results confirmed the suggested structures shown in (**Figs. 1 and 2**).

The thermal stability and purity of ( $\text{I}_1$ - $\text{I}_4$ ) were examined employing combined TG-DSC-MS, and their crystallinity degree was evaluated employing P-XRD. The produced molecules were pure and showed varied thermal stability, they exhibited a semi-crystalline structure, except  $\text{I}_2$  which presented a crystalline structure.

*Due to the enantiomeric properties of  $\text{I}_3$  and  $\text{I}_4$ , which were revealed by their similar FTIR, P.XRD, and TG.DSC.MS results, besides presenting the same specific light deviation value in opposite signs (polarimetry), only  $\text{I}_3$  will be used for further layer applications.*



**Fig. 1:** Synthesis of C-dec-9-enylcalix[4]resorcinarene (**I<sub>1</sub>**) and C-undecylcalix[4]resorcinarene (**I<sub>2</sub>**)

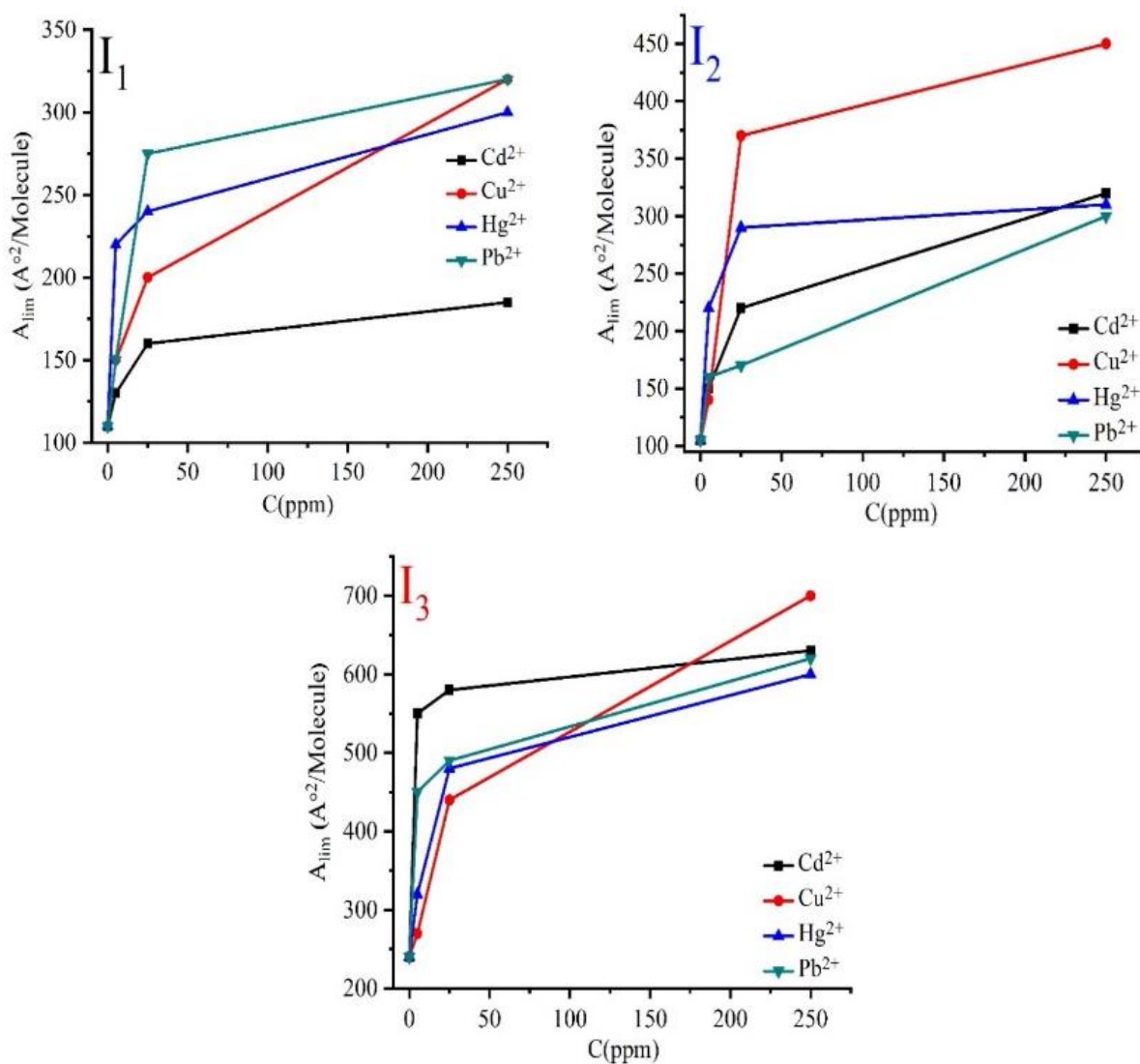


**Fig. 2:** Synthetic procedure of C-dec-9-enylcalix[4]resorcinarene-O-(S)- $\alpha$ -methylbenzylamine (**I<sub>3</sub>**), and C-dec-9-enylcalix[4]resorcinarene-O-(R)- $\alpha$ -methylbenzylamine (**I<sub>4</sub>**)

## Langmuir analyses

### Limiting area variations

The variations of  $A_{lim}$  (Limiting area/molecule: acquired via extrapolation of the Langmuir isotherm's linear part on the 'x' axis) are a robust indication of the interactions occurring at the monolayer/subphase level. While using ionophores as ultra-thin films for potential detection applications targeting heavy metals (HMs), complexation reactions between the ionophores and the HMs are translated by an  $A_{lim}$  increase while adjusting the HMs amounts. Though, depending on the favorable electronic interactions, ionic selectivity towards the ions present in the subphase is performed by the ionophores. **Fig. 3** is supporting this statement by presenting the  $A_{lim}$  dependence on the HMs amounts for ionophores I<sub>1</sub>-I<sub>3</sub>.



**Fig. 3:** Limiting area dependence on heavy metals amounts for ionophores I<sub>1</sub>-I<sub>3</sub>

The noteworthy systematic increase in terms of limiting area is disclosing the high inclusion taking place at the water/air interface level, it indicates similarly that all ionophores were capable of binding to various cations from one side, and demonstrates the incorporation and integration (Via complexation reactions and electrostatic interactions) of these cations within the resorcinarene monolayers from another. Based on the limiting area variations, ionic selectivity is distinguished, specifically as follows:

Order of  $A_{lim}$  for  $I_1$ :  $(I_1)\text{-Pb}^{2+} > (I_1)\text{-Hg}^{2+} > (I_1)\text{-Cu}^{2+} > (I_1)\text{-Cd}^{2+}$

Order of  $A_{lim}$  for  $I_2$ :  $(I_2)\text{-Cu}^{2+} > (I_2)\text{-Hg}^{2+} > (I_2)\text{-Cd}^{2+} > (I_2)\text{-Pb}^{2+}$

Order of  $A_{lim}$  for  $I_3$ :  $(I_3)\text{-Cd}^{2+} > (I_3)\text{-Pb}^{2+} > (I_3)\text{-Hg}^{2+} > (I_3)\text{-Cu}^{2+}$

### ***Interfacial complexation mechanism***

On account of the resorcinarenes' amphiphilic characteristics, enclosing all at once hydrophilic and hydrophobic parts, this key parameter is present. The prospective orientation assumptions of ligands  $I_1$ - $I_3$  is manifesting in a cone conformation at the interface level, supported by hydrogen bindings between the subphase-water molecules and the resorcinols' hydroxyl ( $I_1$ - $I_3$ ) and amine groups ( $I_3$ ), other substituents as alkene and alkane chains are hydrophobic and supposed to front the air, while the ionophores' common ring is parallel to the water-air interface.

### ***Detection of heavy metal ions***

Based on the ionophores ( $I_1$ - $I_3$ ), detection platforms were fabricated on the gold sensing area of the quartz crystal resonators (QCRs) and screen-printed electrodes (SPEs) for the quantification of the heavy metals in aqueous solutions via quartz crystal with impedance measurements (QCM-I) and electrochemical techniques.

### ***QCM-I results***

This section gives insights on outcomes from static in-situ QCM-I measurements applied to detect heavy metals in water samples, first unmodified (Bare) quartz crystal resonators were used, and later, resorcinarene-modified QCM chemosensors were employed. Data in the form of frequency (F), dissipation (D), and the Full Width at Half Maximum (FWHM) variations were collected.

### ***Effect of heavy metals on the gold surface of quartz crystals***

A first step towards the sensing application is to study the effect of the heavy metals on bare crystals upon adding rising amounts of ions ( $\text{Cd}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Hg}^{2+}$ , and  $\text{Pb}^{2+}$ ). For that reason,

frequency, dissipation, and FWHM shifts were recorded on unmodified quartz crystals through in-situ QCM-I measurements.

The quartz resonators' gold electrodes did not detect toxic metals, as no decrease in frequency (Mass loading on the QC surface) was noted for all cases. A rigid character of the electrodes' surfaces was dominant, as no changes in dissipation energy were obvious ( $\Delta D \sim 0$ ). Though, some fluctuations were existing in the majority of plots, explained by the dry electrode's surface wetting due to straight exposure to aqueous solutions. The inability of bare gold surfaces to sense heavy metals proves that neither physical nor chemical modification or interaction has occurred, the later interactions are essential in increasing the quartz crystal's sensitivity, where taking advantage of detection networks is compulsory.

#### ***Heavy metals concentration effect on resorcinarene-based piezogravimetric sensors***

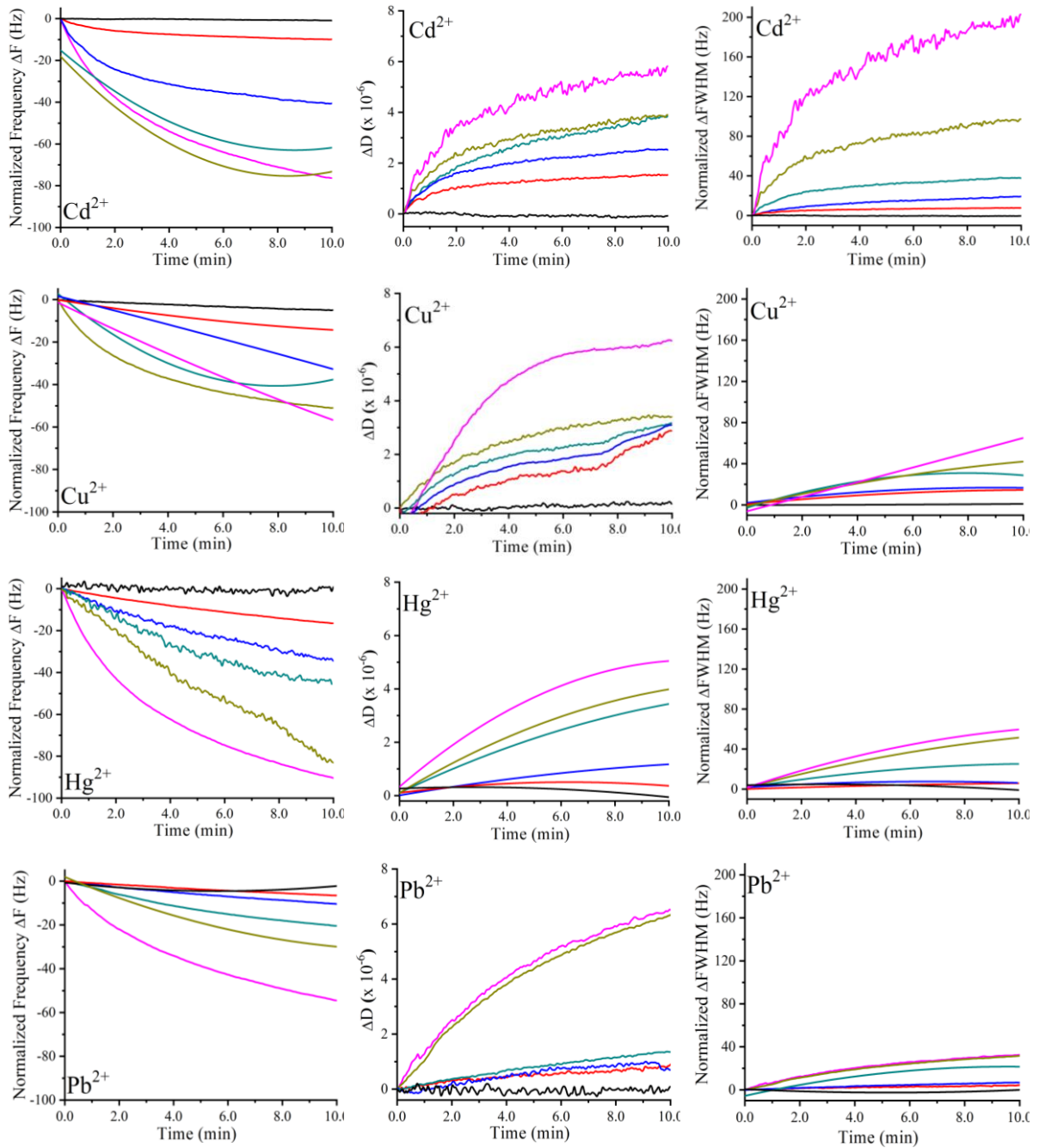
Targeting water environmental monitoring via applied in-situ QCM-I analysis, drop-coated QC gold electrodes using ionophores I<sub>1</sub>, I<sub>2</sub>, I<sub>3</sub> as sensing platforms were constructed, aiming at evaluating their HM detection capacities in model solutions modified via adding toxic metallic elements. Therefore, **Fig. 4** shows the sensing shifts (frequency, dissipation, and FWHM) of I<sub>1</sub> chemosensor against increasing heavy metals concentrations in time.

The heavy metals sensing through the introductory application of resorcinarene-piezogravimetric sensors disclosed its success since the decrease in frequency with increasing the ions amounts is directly related to the mass loading on the sensor's surface. Another feature confirming this prospect is the FWHM variation (Basis of a QCM-I measurement), showing a simultaneous increase, commonly the crystal's loading drives to the above-discussed shifts.

#### ***Ionophores' affinity toward heavy metals***

The FWHM shifts of QCM-I sensors coated with ionophores I<sub>1</sub>-I<sub>3</sub> for the affinity evaluation toward Pb<sup>2+</sup>, Hg<sup>2+</sup>, Cd<sup>2+</sup>, and Cu<sup>2+</sup> in aqueous solution, were plotted in the form of Radar plots, the variations in FWHM are offered for each heavy metal ion (Cd<sup>2+</sup>, Hg<sup>2+</sup>, Pb<sup>2+</sup>, and Cu<sup>2+</sup>), at each concentration (5, 25, 250, 500, and 1000 ppm), and combining the response of the calixresorcinarenes at the same time, this approach is advantageous to understand the chemosensors' detection performances.





**Fig. 4:** The detection sensing shifts ( $\Delta F_n$ ,  $\Delta D_n$ , and  $\Delta FWHM_n$ ) for ionophore I<sub>1</sub> sensor for various heavy metals concentrations (0, 5, 25, 250, 500, and 1000 ppm) in time.

The detection sensing shifts ( $\Delta FWHM_n$ ) are illustrated as radar plots for I<sub>1</sub>, I<sub>2</sub>, I<sub>3</sub>, as shown in **Figs. 5, 6, 7, and 8**. From **Fig. 5**, I<sub>1</sub> displayed the highest detection sensitivity toward Cd<sup>2+</sup> ions at all tested concentrations while I<sub>2</sub> was effective at lower concentrations (5 and 25 ppm). As the concentration of cations increased, the sensitivity of I<sub>2</sub> decreased slightly. I<sub>3</sub> produced low sensitivity at all concentrations.

Similarly, **Fig. 6** is related to the detection of  $\text{Cu}^{2+}$  ions by ionophores  $\text{I}_1$ - $\text{I}_3$  at different concentrations. It showed that again  $\text{I}_1$  produced the best detection sensitivity all over the concentration range and the detection increased by increasing the  $\text{Cu}^{2+}$  concentration.  $\text{I}_2$  showed good detection at concentrations above 500 ppm while low detection at lower concentrations.  $\text{I}_3$  showed a slight increase at the 1000 ppm concentration range.

**Fig. 7** shows the detection of  $\text{Hg}^{2+}$  ions. As illustrated in **Fig. 7**,  $\text{I}_2$  displayed the highest detection sensitivity at all tested concentrations while  $\text{I}_1$  had high detection at concentrations above 250 ppm. Ionophore  $\text{I}_3$  displayed moderate detection at lower concentration values.

The case of  $\text{Pb}^{2+}$  ions detection by  $\text{I}_1$ - $\text{I}_3$  is shown in **Fig. 8**. Similar to the case of  $\text{Hg}^{2+}$ ,  $\text{I}_2$  once again is the most sensitive at all concentrations, while  $\text{I}_1$  was more effective as the ions concentration was increased. Ionophore  $\text{I}_3$  had moderate and low detections.

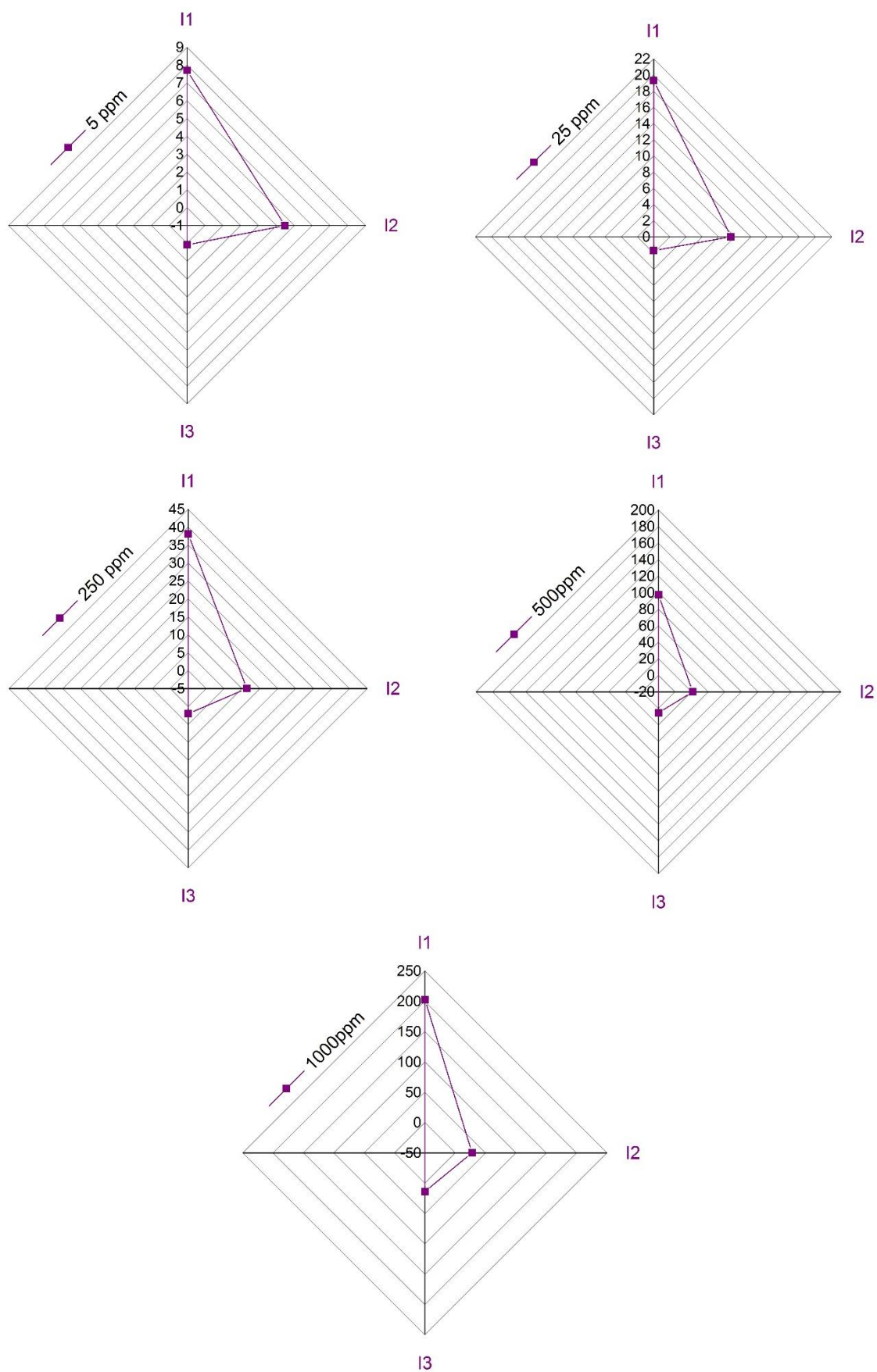
From the above observations, it is clear that the proposed approach is recommended to comprehend the sensing behavior and affinities of different oligomers towards heavy metals ions in aqueous solutions. When comparing responses of the studied potential sensors, it's revealed that  $\text{I}_3$  had moderate detection ability towards all heavy metals ions with selective preferences, though compounds  $\text{I}_1$  and  $\text{I}_2$  had significantly powerful interactions and high binding affinities.

### *Sensing characteristics for the Calix-QCM platforms*

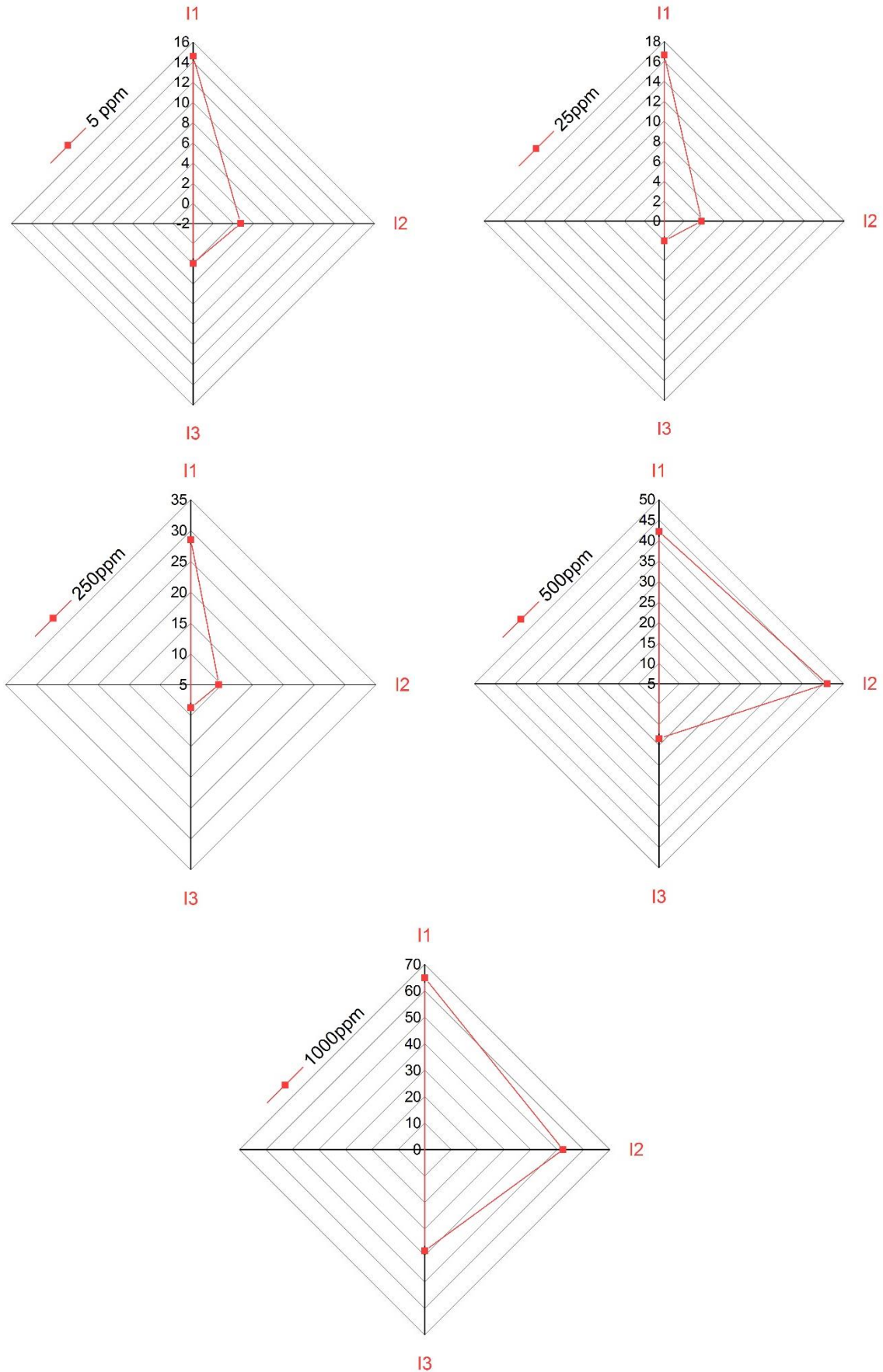
Clean quartz crystals were modified using ( $\text{I}_1$ - $\text{I}_3$ ) and were employed as detection platforms via monitoring the frequency and FWHM shifts. The piezogravimetric sensors successfully detected the heavy metals and detection limits (LODs) in the ppm/ppb level were attained (**Table 1**). The lowest LODs were associated with  $\text{Cu}^{2+}$  for  $\text{I}_1$  (10.00 ppb), and  $\text{Pb}^{2+}$  ions for  $\text{I}_2$  (0.48 ppm) and  $\text{I}_3$  (0.45 ppm).

**Table 1:** Metrological parameters of Calix-QCM sensors based on frequency and FWHM.

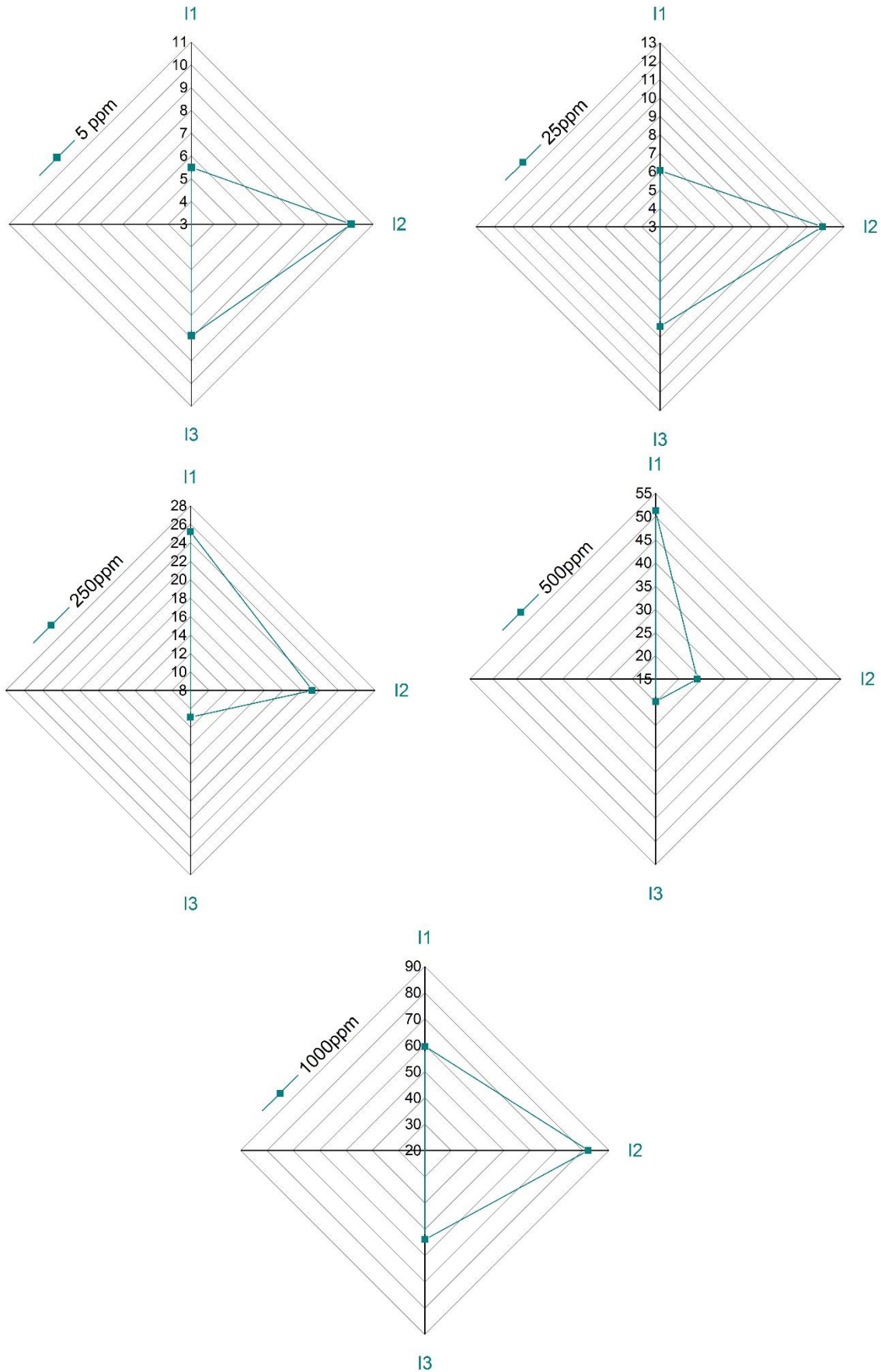
Ionophores	HM ions	LR (ppm)	$\Delta F_n/n$			$\Delta FWHM_n/n$			
			S (Hz/ppm)	LOD (ppm)	LOQ (ppm)	LR (ppm)	S (Hz/ppm)	LOD (ppm)	LOQ (ppm)
$\text{I}_1$	$\text{Cd}^{2+}$	2-25	1.571	0.61	1.83	250-1000	0.225	0.32	0.96
	$\text{Cu}^{2+}$	0.5-25	1.056	0.01	0.03	2-1000	0.052	0.57	1.71
	$\text{Hg}^{2+}$	3-25	1.215	0.88	2.64	1-500	0.093	0.37	1.11
	$\text{Pb}^{2+}$	2-1000	0.045	0.47	1.42	3-500	0.057	0.89	2.67
$\text{I}_2$	$\text{Cd}^{2+}$	5-25	0.215	1.82	5.46	5-1000	0.021	1.63	4.90
	$\text{Cu}^{2+}$	250-1000	0.554	0.87	2.61	1-250	0.028	0.18	0.54
	$\text{Hg}^{2+}$	5-250	0.039	2.53	7.59	3-500	0.030	0.76	2.28
	$\text{Pb}^{2+}$	2-500	0.080	0.48	1.46	1-1000	0.048	0.20	0.60
$\text{I}_3$	$\text{Cd}^{2+}$	5-500	0.040	1.50	4.50	3-1000	0.009	0.89	2.96
	$\text{Cu}^{2+}$	5-1000	0.010	0.93	2.79	1-1000	0.038	0.20	0.66
	$\text{Hg}^{2+}$	3-25	1.171	0.99	2.99	0.5-1000	0.030	0.11	0.36
	$\text{Pb}^{2+}$	25-1000	0.008	0.45	1.35	5-1000	0.034	1.77	5.31



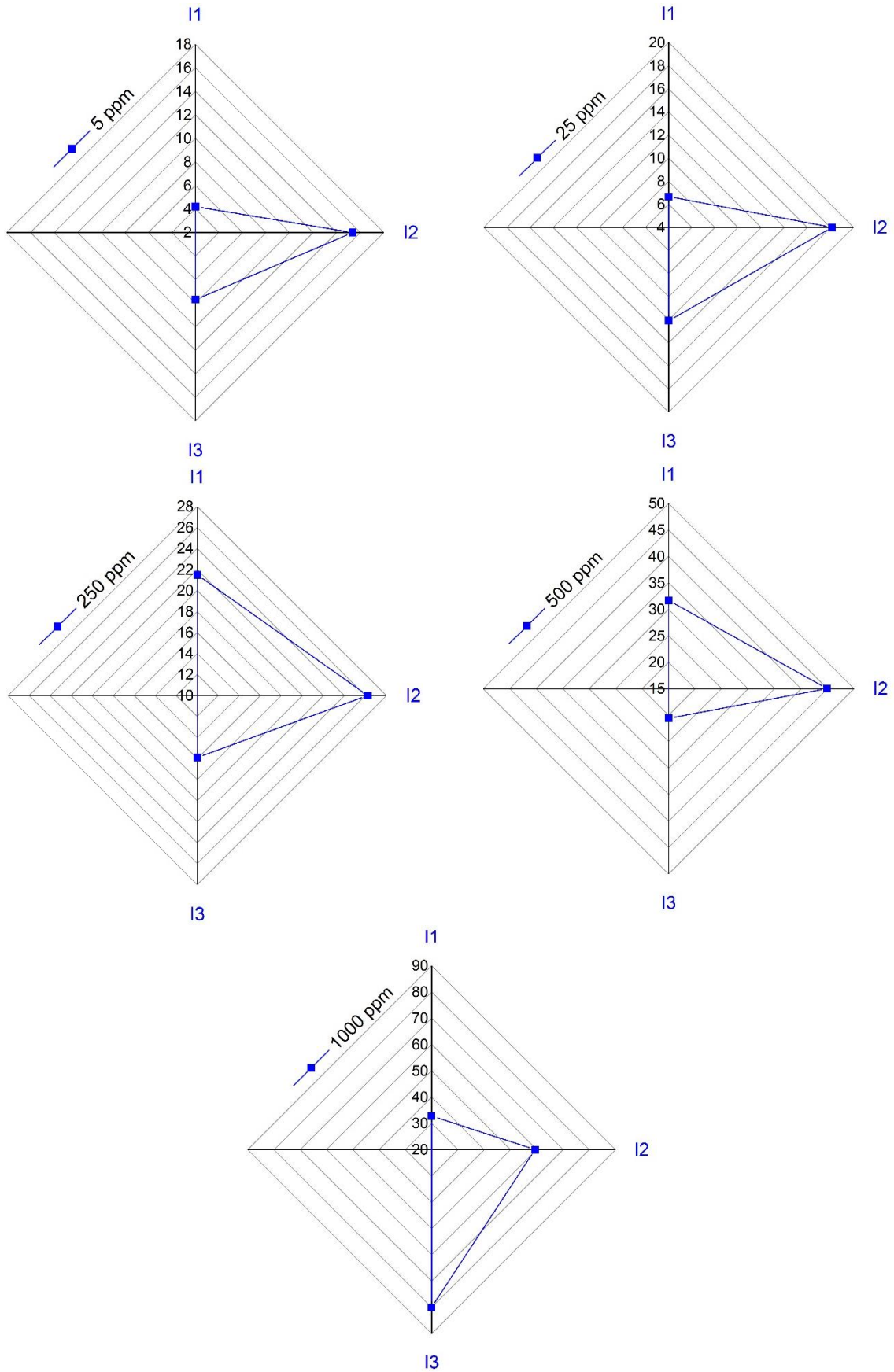
**Fig. 5:** Full width at half maximum variations of the Calix-QCM chemosensors (I<sub>1</sub>, I<sub>2</sub>, I<sub>3</sub>) for different concentrations (5, 25, 50, 500, and 1000 ppm) of  $\text{Cd}^{2+}$ .



**Fig. 6:** Full width at half maximum variations of the Calix-QCM chemosensors (I<sub>1</sub>, I<sub>2</sub>, I<sub>3</sub>) for different concentrations (5, 25, 50, 500, and 1000 ppm) of  $\text{Cu}^{2+}$ .



**Fig. 7:** Full width at half maximum variations of the Calix-QCM chemosensors (I<sub>1</sub>, I<sub>2</sub>, I<sub>3</sub>) for different concentrations (5, 25, 50, 500, and 1000 ppm) of  $Hg^{2+}$ .



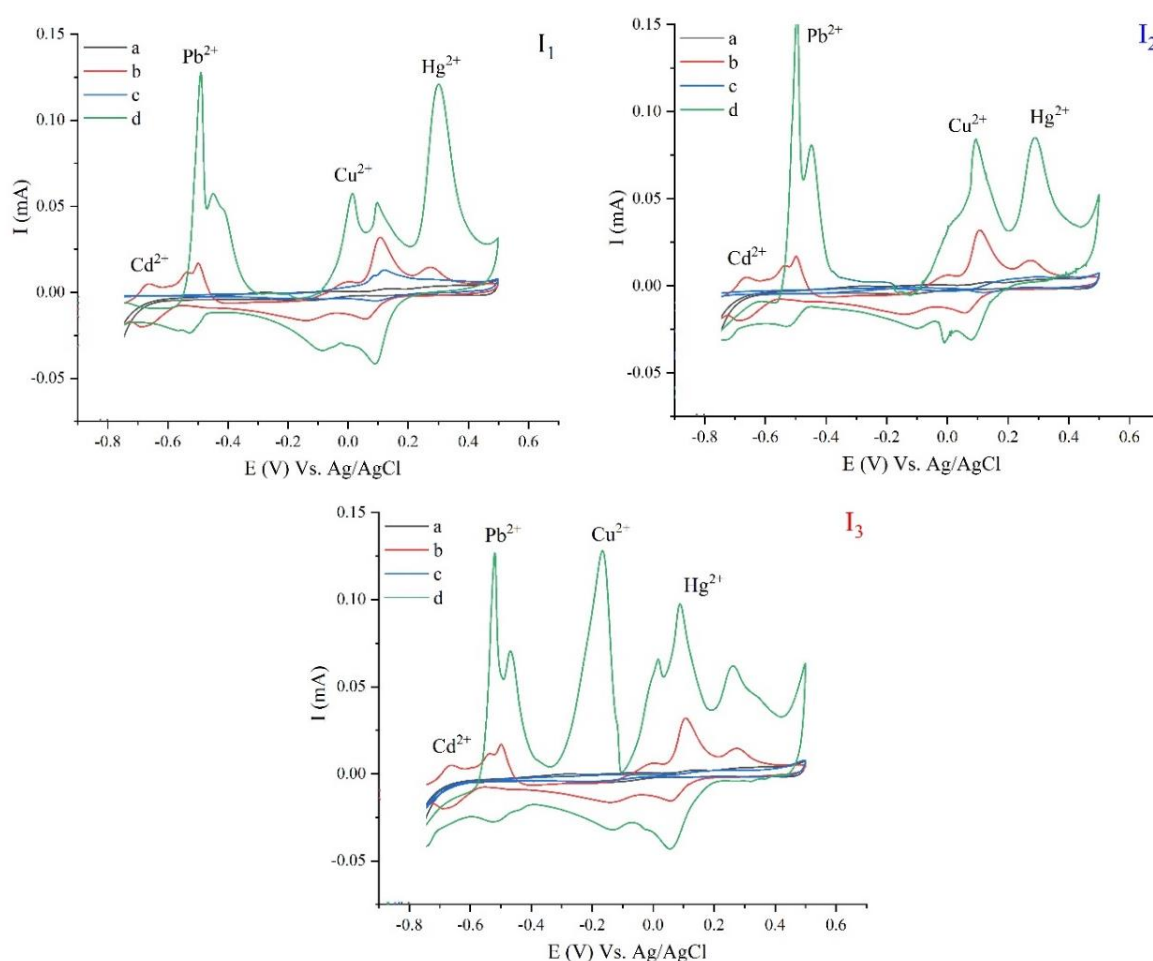
**Fig. 8:** Full width at half maximum variations of the Calix-QCM chemosensors (I<sub>1</sub>, I<sub>2</sub>, I<sub>3</sub>) for different concentrations (5, 25, 50, 500, and 1000 ppm) of  $Pb^{2+}$ .

## Electrochemical results

### Electrochemical characterization

#### Cyclic voltammetry (CV) and Square wave voltammetry (SWV)

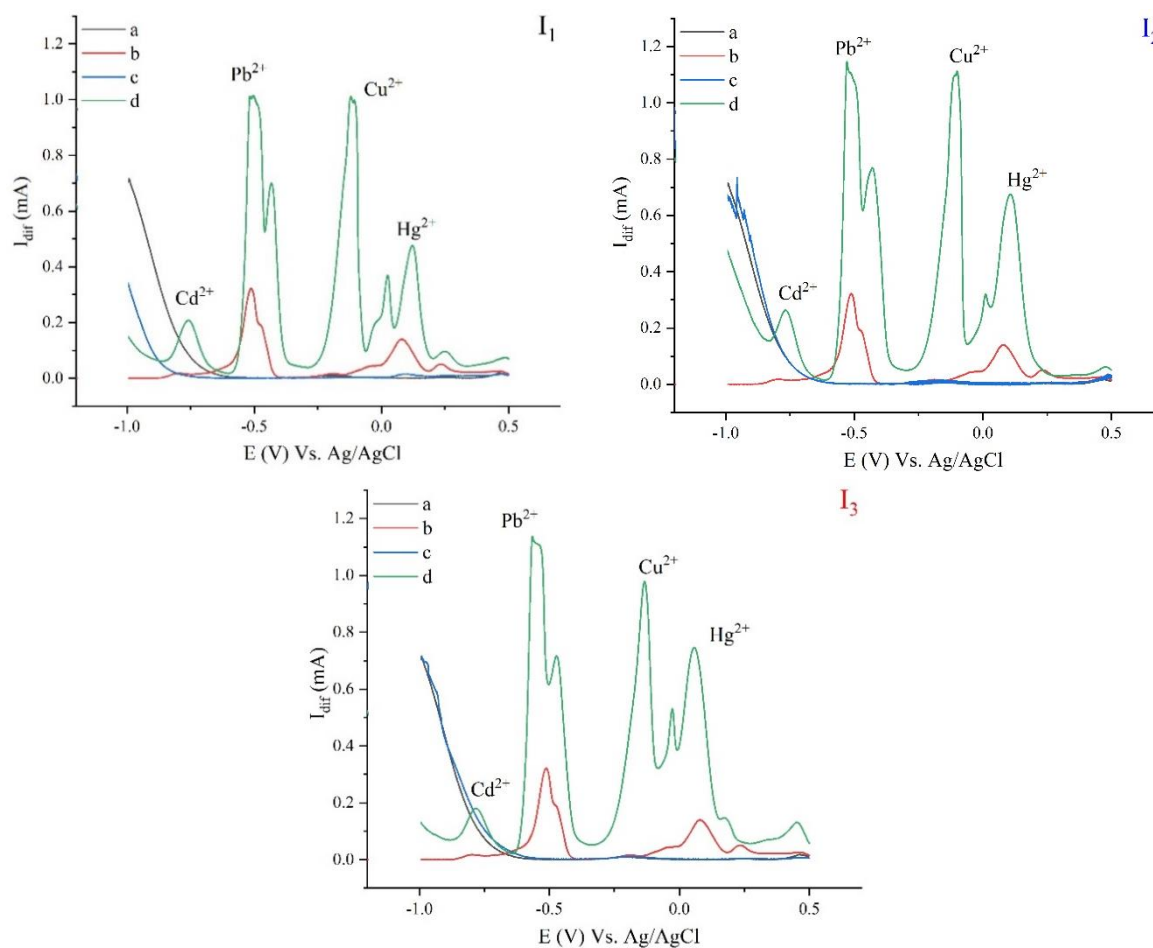
The electrochemical behavior of the sensing platforms was preliminarily examined employing CV. **Fig. 9** presents the CV signatures of the bare and modified electrodes in the presence and absence of ions. As displayed in **Fig. 9**, no significant analytical signals (Redox peaks) appeared in the absence of ions for the bare (**a**) and modified electrodes (**c**) in 0.2 M HCl. While, bare gold electrodes (**b**) presented moderate responses when the ions were added to the electrolytic medium, and further modifications of the electrodes with ionophores I<sub>1</sub>-I<sub>3</sub> (**d**) have enhanced the well-defined oxidation current peaks of heavy metals on their respective potentials. However, the cathodic reduction peaks of heavy metals are not well-separated and intense as the anodic ones.



**Fig. 9:** Overlaid voltammograms of a) bare electrodes in 0.2 M HCl, b) bare electrodes in the presence of 1 ppm each of heavy metals in 0.2 M HCl, c) modified electrodes in 0.2 M HCl, d) modified electrodes in the presence of 1 ppm each of heavy metals in 0.2 M HCl.

The detected increase in the CV current peaks of heavy metals after the modification of electrodes is owing to the fast electron-transfer rate at the ionophores@electrodes platforms and their conductive nature, besides the complexation or chelation process between the ions in electrolytic medium and the impregnated resorcinarenes in the electrodes.

The SWV signatures of the bare and modified electrodes in the presence and absence of heavy metals were also studied to complement the CV characterization and are shown in **Fig. 10**



**Fig. 10:** SWV signatures of a) bare electrodes in 0.2 M HCl, b) bare electrodes in the presence of 1 ppm each of heavy metals in 0.2 M HCl, c) modified electrodes in 0.2 M HCl, d) modified electrodes in the presence of 1 ppm each of heavy metals in 0.2 M HCl.

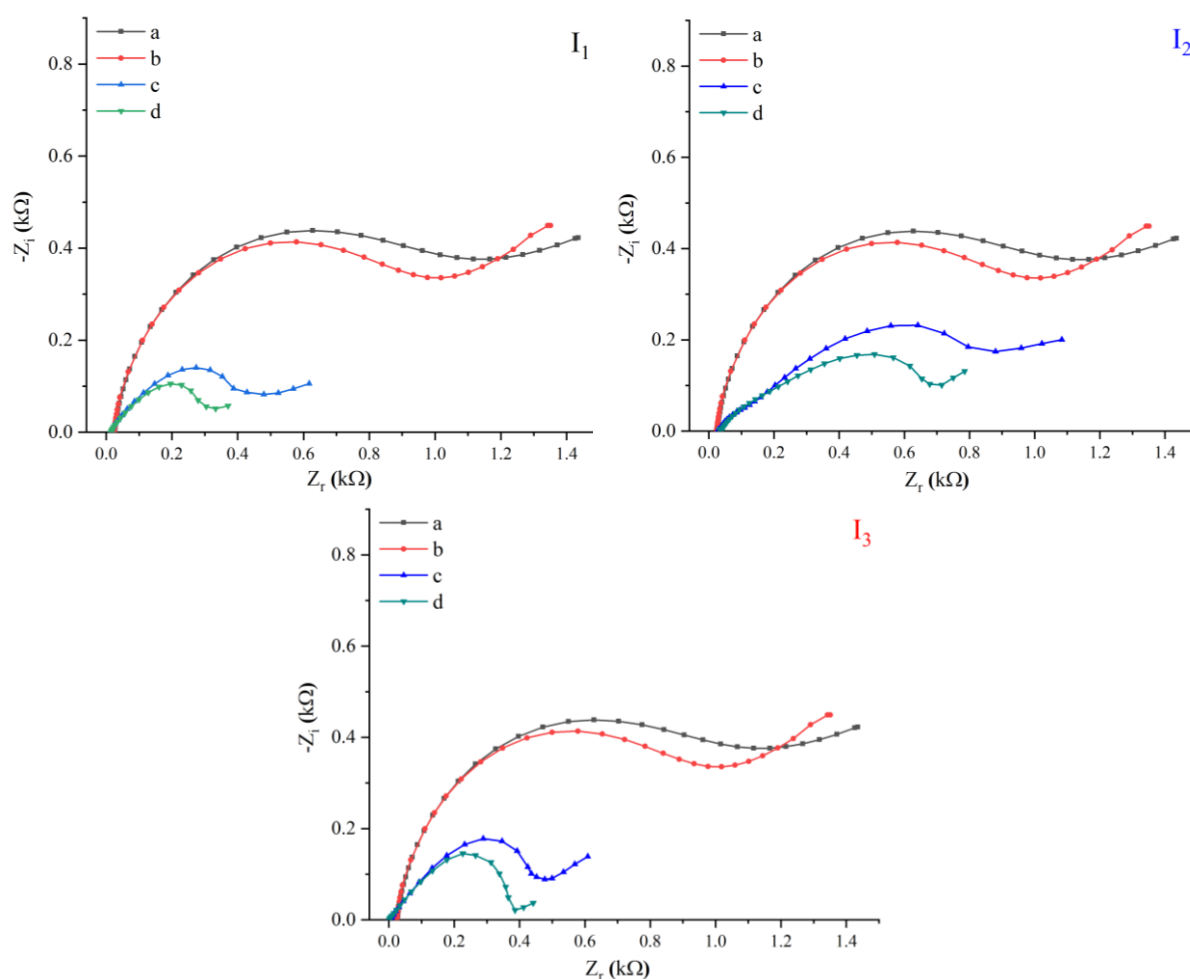
The SWV signatures are in decent agreement with the CV results, where the bare (a) and modified electrodes (c) did not represent any anodic signal. After adding the heavy metals to the medium, the appearance of net well-separated peaks of heavy metals centered at their pertaining potentials was noticed with enhanced current intensity when coming to the ionophores@electrodes (d) compared to the bare gold electrodes (b), meaning that the sensitivity of the electrodes has increased notably after their modification, owing to the heavy



metals accumulation on their surfaces, the high adsorption capacity, and the large electroactive surface of resorcinarenes platforms.

### **Electrochemical impedance spectroscopy (EIS)**

The EIS technique was employed for characterizing the interface (solution/electrodes surfaces), the gained EIS outcomes were plotted in a Nyquist diagram form showing the real and imaginary parts of the impedance (**Fig. 11**). The Nyquist plots displayed a semicircle in the high frequencies associated with an electron transfer limited process, and a further line at low frequencies, indicating a diffusion-controlled process.



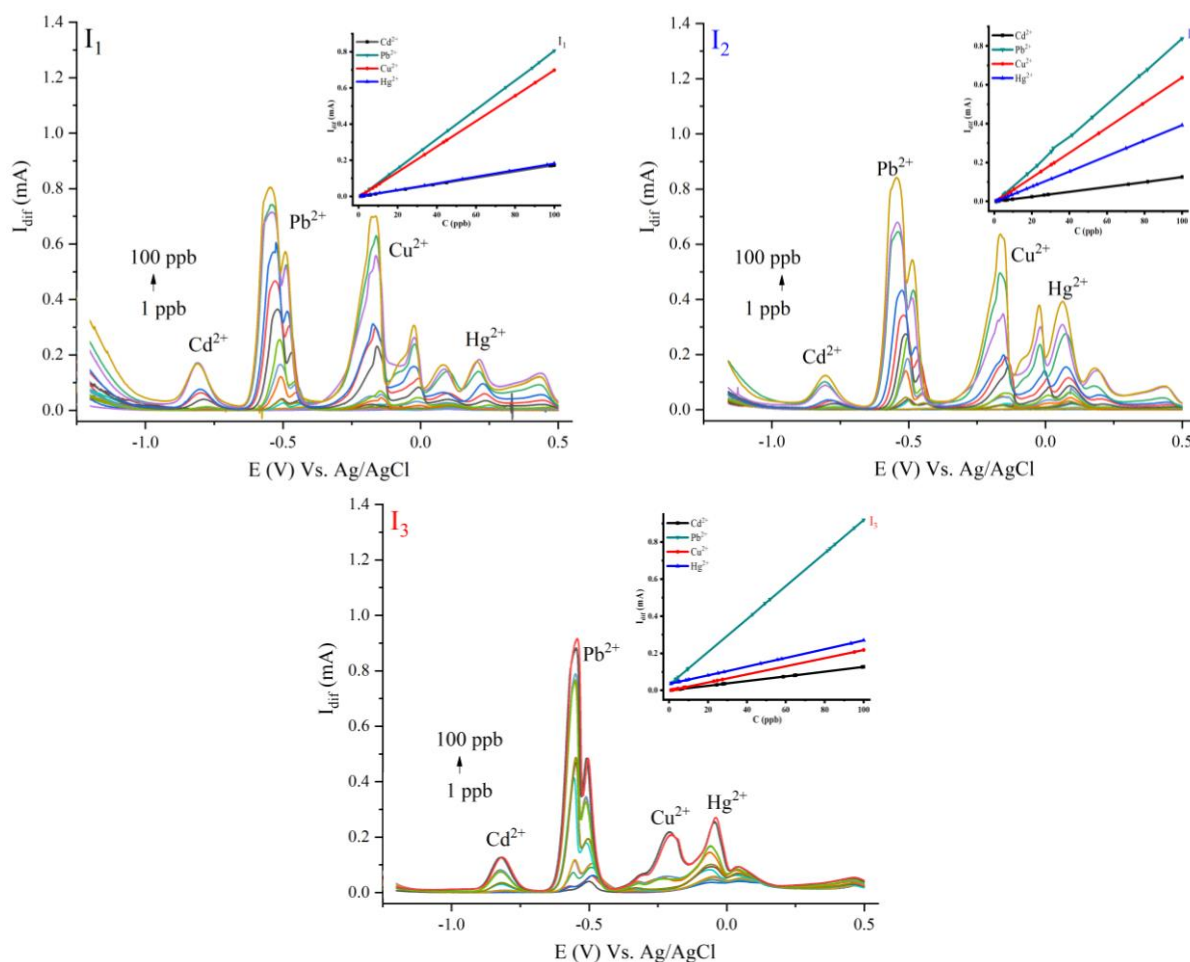
**Fig. 11:** EIS Nyquist plots of **a)** bare electrodes in 0.2 M HCl, **b)** bare electrodes in the presence of 1 ppm each of heavy metals in 0.2 M HCl, **c)** modified electrodes in 0.2 M HCl, **d)** modified electrodes in the presence of 1 ppm each of heavy metals in 0.2 M HCl.

In the case of bare electrodes **Fig. 11 (a)** and **(b)**, the semicircle diameter equal to the charge transfer resistance ( $R_{ct}$ ) decreased after the addition of 1 ppm of heavy metals in 0.2 M HCl. Further decrease in  $R_{ct}$  was revealed after modifying the electrodes' surfaces with different ionophores **Fig. 11 (c)** and **(d)**. The smallest  $R_{ct}$  values were associated with the modified

electrodes in the presence of 1 ppm of heavy metals in 0.2 M HCl (**d**). The decrease in  $R_{ct}$  values of the modified electrodes indicates the electrode surface conductivity improvement from one side and the enhanced electron transfer properties from another.

### **Electrochemical determination of heavy metals**

The analytical performance of the proposed electrochemical sensors was examined under the determined optimal conditions (0.2 M HCl (pH = 0.7), accumulation potential of -1.2 V for an accumulation time of 90 s). **Fig. 12** presents the overlaid square wave voltammograms (SWV) for the simultaneous electrochemical determination of heavy metals (HMs) in the concentration range from 1 to 100 ppb based on the  $I_1$ - $I_3$ @Screen printed electrodes (SPEs), whereas the corresponding calibration curves are displayed as inserts.



**Fig. 12:** Simultaneous electrochemical determination of the studied heavy metals in the concentration range from 1 to 100 ppb under optimal conditions based on  $I_1$ - $I_3$  modified electrodes, the inserts are presenting for the corresponding calibration curves.

The peak separation in the SWV signals is large to quantify each metal ion distinctly. On the voltammograms of  $I_1$ @SPE and  $I_2$ @SPE, some peaks appeared apart from those corresponding

to the heavy metals, owing either to non-complexed analytes trapped on the modified SPEs surfaces (electroactive impurities formerly present in the electrolytic solution) or due to the resorcinarenes' leaching. Based on the constructed calibration curves (**Fig. 12**), a perfect linear relationship between the concentrations of heavy metals and the responses in peak currents was established (**Table. 2**). The limits of detection (LODs) and limits of quantification (LOQs) were calculated from  $LOD = 3.3\sigma/S$  and  $LOQ = 10\sigma/S$ , where  $\sigma$  is the standard deviation of the blank (based on three measurements) and S is the linear range's slope, or else the sensitivity.

**Table 2:** Metrological parameters of resorcinarenes@SPE sensors based on SWV signals.

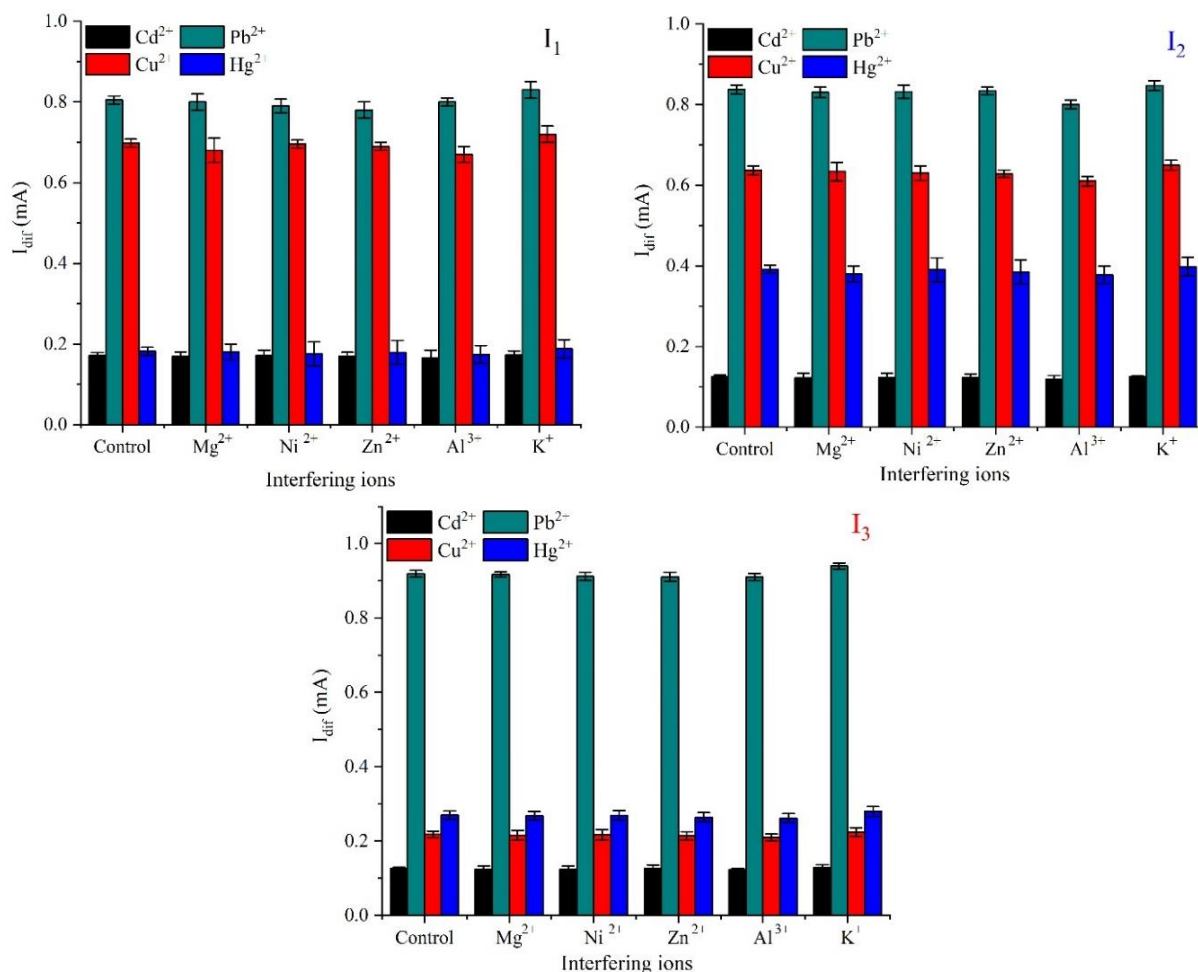
Ionophore	HM	LR (ppb)	LOD (ppb)	LOQ (ppb)
I <sub>1</sub>	Cd <sup>2+</sup>	1-100	0.37	1.11
	Pb <sup>2+</sup>	1-100	0.19	0.57
	Cu <sup>2+</sup>	1-100	0.23	0.70
	Hg <sup>2+</sup>	1-100	0.41	1.23
I <sub>2</sub>	Cd <sup>2+</sup>	1-100	0.39	1.17
	Pb <sup>2+</sup>	1-100	0.17	0.51
	Cu <sup>2+</sup>	1-100	0.25	0.75
	Hg <sup>2+</sup>	1-100	0.29	0.87
I <sub>3</sub>	Cd <sup>2+</sup>	1-100	0.38	1.14
	Pb <sup>2+</sup>	1-100	0.15	0.45
	Cu <sup>2+</sup>	1-100	0.33	0.99
	Hg <sup>2+</sup>	1-100	0.31	0.93

The proposed sensors presented wide linear responses, the attained LODs and LOQs are much lower than the recommended thresholds stated by the WHO and the USEPA, therefore confirming the ultra-sensitivity of our sensing platforms.

### **Interferences study**

The effect of interfering ions on the heavy metals determination and the sensors' selectivity was investigated via adding metal ions frequently present in water matrices, i.e. Al<sup>3+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Zn<sup>2+</sup>, and Ni<sup>2+</sup>. A 4 ppm concentration (40 folds) of each interfering ion was added to 0.2 M HCl (pH = 0.7) containing 100 ppb of heavy metals, **Fig. 13** is therefore displaying a comparison of the heavy metals peak currents for the developed sensors in the absence (control) and in the presence of interfering ions under the determined optimal conditions.

Analyzing **Fig. 13** and **Table 3**, the calculated signal deviations of 100 ppb of heavy metals are less than 5%, so the studied interfering cations did not affect the simultaneous detection of heavy metals while applying the optimized procedure, which withstands the potential employment of our sensors for the simultaneous selective determination of heavy metals.



**Fig. 13:** Bar charts representing the heavy metals peak currents for the  $I_1$ - $I_3$ @SPEs sensors in the absence (control) and the existence of interfering ions under optimal conditions.

**Table 3:** Current peak deviations for 100 ppb of HM in the presence of 40 folds' excess of interfering ions.

Ionophores	Interfering ions	Peak deviation (%) = $\left(\frac{I_{control} - I_{control+interfering}}{I_{control}}\right) \times 100$			
		Cd <sup>2+</sup>	Pb <sup>2+</sup>	Cu <sup>2+</sup>	Hg <sup>2+</sup>
<b>I<sub>1</sub></b>	Mg <sup>2+</sup>	1.17	0.62	2.57	1.10
	Ni <sup>2+</sup>	0.58	1.86	0.30	3.84
	Zn <sup>2+</sup>	1.17	3.10	1.15	1.64
	Al <sup>3+</sup>	4.06	0.62	4.01	-4.40
	K <sup>+</sup>	-0.60	-3.11	-3.15	-3.29
<b>I<sub>2</sub></b>	Mg <sup>2+</sup>	2.40	0.95	0.47	3.06
	Ni <sup>2+</sup>	1.60	0.72	1.10	0.51
	Zn <sup>2+</sup>	0.80	0.47	1.26	1.78
	Al <sup>3+</sup>	4.80	4.53	4.23	3.83
	K <sup>+</sup>	-0.56	-1.07	-2.04	-1.53
<b>I<sub>3</sub></b>	Mg <sup>2+</sup>	1.57	0.21	0.91	0.74
	Ni <sup>2+</sup>	2.36	0.76	0.45	0.37
	Zn <sup>2+</sup>	0.78	0.87	1.83	2.22
	Al <sup>3+</sup>	3.15	0.98	3.66	2.96
	K <sup>+</sup>	-1.96	-2.28	-2.75	-3.70

### ***Examination of reproducibility and repeatability***

Under optimized conditions, the sensors' reproducibility has been evaluated employing three modified electrodes for each ionophore to simultaneously detect 100 ppb of heavy metals. Likewise, for the examination of repeatability, utilizing one modified electrode for each ionophore, three successive square wave voltammetric scans were performed to quantify 100 ppb of heavy metals. The outcomes in terms of residual standard deviation (RSD) are tabulated in **Table 4**. The RSDs did not pass 5 %, indicating excellent reproducibility and repeatability of the developed sensors, and so their potential practical utilization to determine trace levels of heavy metals simultaneously with high analytical selectivity.

**Table 4:** RSDs related to reproducibility and repeatability of the developed sensors.

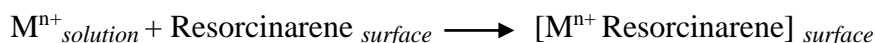
Ionophore	RSD related to reproducibility				RSD related to repeatability			
	Cd <sup>2+</sup>	Pb <sup>2+</sup>	Cu <sup>2+</sup>	Hg <sup>2+</sup>	Cd <sup>2+</sup>	Pb <sup>2+</sup>	Cu <sup>2+</sup>	Hg <sup>2+</sup>
<b>I<sub>1</sub></b>	4.68	3.93	3.64	3.24	2.19	2.56	1.44	2.18
<b>I<sub>2</sub></b>	4.78	3.71	3.55	4.84	2.93	2.12	3.24	2.56
<b>I<sub>3</sub></b>	3.12	4.34	4.31	4.73	3.73	2.73	2.54	3.77

### ***Heavy metals ions detection mechanisms***

#### ***Piezogravimetric detection process***

Numerous factors must be involved in explaining the detection mechanism, for instance, the complementarity between metal ions and resorcinarene cavity sizes, besides the molecular structure of ligands (substituents nature and number). Potential complexation interactions between sensing platforms and target ions are mainly of a non-covalent physical nature (*VDW*, cation- $\pi$ ...etc.). Herein, we enlighten the sensing mechanism in two major phases:

- A first phase manifesting in a complexation, or else host-guest interaction between the metals ions ( $M^{n+} = Cd^{2+}, Cu^{2+}, Hg^{2+},$  and  $Pb^{2+}$ ) and the resorcinarenes (**I<sub>1</sub>**, **I<sub>2</sub>**, and **I<sub>3</sub>**) already attached to the gold surface, either owing to an electron transfer from heteroatoms and nucleophilic elements towards heavy metals or due to their physical adsorption within the ligands' cavities, commonly these interactions are of *VDW* and cation- $\pi$  origins:



- A second phase is the mass loading (accumulation) of metals ions on the solution-electrode interface, and the piezogravimetric detection thanks to the metal ions buildup on the resonator's surface.

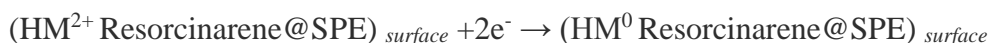
### ***Electrochemical detection process***

The proposed sensing platforms could achieve low detection limits due to the analytical performance improvement; explained by the high complexation affinity between the heavy metals and the hydroxyl groups of the resorcinarenes plus the lone pair of electrons on the oxygen and nitrogen atoms (I<sub>3</sub>), affording better conditions for a host-guest reaction, the suggested electrochemical mechanism can be clarified in three steps [125]:

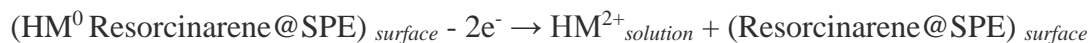
1. **Accumulation**: Physical adsorption of charged heavy metals (HMs) on the modified electrodes' surfaces (SPEs), mainly via electrostatic attractions:



2. **Preconcentration**: At a higher negative potential compared to that of the HM<sup>2+</sup>/HM couples, the adsorbed HMs are electrodeposited on the modified SPEs through a cathodic reduction from a valence state of (2<sup>+</sup>) to (0) to enhance the mass transfer rate, permitting the HMs to be deposited at the SPE surface:



3. **Stripping**: the electrodeposited HMs are turned back to the electrolytic solution through anodic oxidation, translated by an SWV analytic signal. In this step, a positive scan took place for the consistent determination of the four HMs:



## New Scientific Results

My thesis work was devoted to the development and application of resorcinarene based ionophores as novel piezogravimetric and electrochemical chemosensing sensor platforms, to detect HMs ions in aqueous solutions. In conformity with the established findings and publications, the following thesis points can be concluded:

**Point 1. A series of Calix[4]resorcinarene oligomers (I<sub>1</sub>-I<sub>4</sub>), comprising two novel ionophores (I<sub>3</sub>, I<sub>4</sub>) bearing chiral moieties, were effectively synthesized based on acid-catalyzed cyclo-condensation reactions.**

*After synthesis of the oligomers, I performed characterization of the oligomers using FTIR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR, TG-DSC-MS, and PXRD, to confirm their structures, thermal stability, purity, and crystalline behavior. Undeniably, an agreement between crystallinity degree and DSC outcomes (melting endotherms' shapes) was prominent.* [publications: 1,4]

**Point 2. I verified the synthesized oligomers' complexation capability and binding preferences towards HM cations (Cd<sup>2+</sup>, Cu<sup>2+</sup>, Hg<sup>2+</sup>, and Pb<sup>2+</sup>) present in the subphase by the Langmuir Π-A isotherms method.**

*Based on the limiting area variations acquired from the Langmuir isotherms, the ionophores showed ionic selectivity as follows: (I<sub>1</sub>)-Pb<sup>2+</sup>, (I<sub>1</sub>)-Hg<sup>2+</sup>, (I<sub>2</sub>)-Cu<sup>2+</sup>, (I<sub>2</sub>)-Hg<sup>2+</sup>, (I<sub>3</sub>)-Cd<sup>2+</sup>, (I<sub>3</sub>)-Pb<sup>2+</sup>. And, the interfacial interaction mechanism is described as a prospective orientation of (I<sub>1</sub>-I<sub>3</sub>) manifesting in a cone conformation at the interface level, supported by hydrogen bindings between the subphase-water molecules containing the heavy metals and the resorcinols' hydroxyl (I<sub>1</sub>-I<sub>3</sub>) and amine groups (I<sub>3</sub>), other substituents as alkene and alkane chains are hydrophobic and supposed to front the air, while the ionophores' common ring is parallel to the water-air interface.* [publications: 3,5]

**Point 3. I successfully applied the newly developed QCM-I with the impedance measurement analyses (FWHM deviation) by fabricating mass-sensitive resorcinarene (I<sub>1</sub>-I<sub>3</sub>) chemosensors for detecting Cd<sup>2+</sup>, Cu<sup>2+</sup>, Hg<sup>2+</sup>, and Pb<sup>2+</sup> ions in aqueous solutions.**

*The piezogravimetric sensors successfully detected the heavy metals and detection limits in the ppm/ppb level were attained. The fabricated sensors displayed high sensing characteristics (Wide linear ranges, high sensitivities, low detection, and quantification limits). Based on FWHM shifts, the ionic selectivity was noticeable: (I<sub>1</sub>)-Cd<sup>2+</sup>, (I<sub>1</sub>)-Hg<sup>2+</sup>, (I<sub>2</sub>)-Cu<sup>2+</sup>, (I<sub>2</sub>)-Pb<sup>2+</sup>, (I<sub>3</sub>)-Cd<sup>2+</sup>, (I<sub>3</sub>)-Hg<sup>2+</sup>. [publications: 4, 5, 6, 7]*

**Point 4. I assembled the Electrochemical sensing platforms based on (I<sub>1</sub>-I<sub>3</sub>) chemosensors and simultaneously detected heavy metals ions via SWV under optimized conditions, where decent detection characteristics (detection limits, sensitivity, selectivity, repeatability, and reproducibility) were achieved.**

*Based on (I<sub>1</sub>-I<sub>3</sub>) sensors, decent sensing characteristics were achieved, reaching detection limits in the ppb level, the lowest ones were associated with Pb<sup>2+</sup> as follows: I<sub>1</sub>= 0.19 ppb, I<sub>2</sub> = 0.17 ppb, I<sub>3</sub>= 0.15 ppb. The sensors' selectivity evaluation was performed by studying the effect of interfering ions majorly present in water sources (Mg<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup>, Al<sup>3+</sup>, and K<sup>+</sup>) on the SWV output signals. The interfering ions did not affect the simultaneous detection of heavy metals (RSD < 5%), and the sensors presented excellent repeatability and reproducibility (RSD < 5%).* **[publication: 8]**

## Future recommendations and applications

In summary, this dissertation has presented a new approach toward the environmental procedures for the detection of heavy metals ions in water. We have evaluated the chemical and physical properties of the investigated chemicals as detecting elements for the dangerous cations. The resulting ideas from this analysis lead to new more efficient considerations to be taken into account in the future works of this project, and we believe that more progress can be made by:

- Suggesting new immobilization approaches for the ionophores on the Au-surface.
- Applying gold nanoparticles in synergetic effect with the ionophores to amplify the frequency signal for the QCM analysis aiming to detect the HMs at a ppb level.
- Overcoming the selectivity limitations concerning the QCM analysis, and studying the effect of interfering ions.
- Elaborating the possibility of using computational calculations and simulations to understand the mechanisms of the detection process.
- Exploring the sensing abilities of the produced ionophores in the gas phase aiming to detect toxic gases.

*This in turn leads to broad practical impact for facilitating environmental protection and avoiding seriously dangerous species in water.*



## List of contributions

### Publications in Scientific Journals

[PR-1] Eddaif, Larbi ; Trif, László ; Telegdi, Judit ; Egyed, Orsolya ; Shaban, Abdul. *Calix[4]resorcinarene macrocycles: Synthesis, thermal behavior, and crystalline characterization. Journal Of Thermal Analysis And Calorimetry* 137 pp. 529-541., 13 p. (2019).  
(Citations:2, IF: 4.626, Q2)

[PR-2] Eddaif, L.; Shaban, A.; Telegdi, J. *Sensitive detection of heavy metals ions based on the calixarene derivatives-modified piezoelectric resonators: a review. International Journal Of Environmental Analytical Chemistry* 99: 9 pp. 824-853. , 30 p. (2019), (Citations: 40, IF: 2.826, Q2)

[PR-3] Eddaif, Larbi; Shaban, Abdul; Telegdi, Judit. *Application of the Langmuir Technique to Study the Response of C-dec-9-en-1-ylcalix[4]resorcinarene and C-undecylcalix[4]resorcinarene Ultra-thin Films' Interactions with Cd<sup>2+</sup>, Hg<sup>2+</sup>, Pb<sup>2+</sup>, and Cu<sup>2+</sup> Cations Present in the Subphase. Water Air And Soil Pollution* 230: 12 Paper: 279 (2019).  
(Citations: 1, IF: 2.520, Q2)

[PR-4] Eddaif, Larbi; Shaban, Abdul; Telegdi, Judit; Szendro, István *A Piezogravimetric Sensor Platform for Sensitive Detection of Lead (II) Ions in Water Based on Calix[4]resorcinarene Macrocyces: Synthesis, Characterization, and Detection. Arabian Journal Of Chemistry* 13: 2 pp. 4448-4461. , 14 p. (2020).  
(Citations:5, IF: 5.165, Q1)

[PR-5] Eddaif, Larbi; Shaban, Abdul ; Szendro, István. *Calix[4]Resorcinarene Macrocyces Interactions with Cd<sup>2+</sup>, Hg<sup>2+</sup>, Pb<sup>2+</sup>, and Cu<sup>2+</sup> Cations: a QCM- I and Langmuir Ultra- thin Monolayers Study. Electroanalysis* 32: 4 pp. 755-766. , 12 p. (2020). (Citations:2, IF: 3.223, Q2)

[PR-6] Shaban, Abdul; Eddaif, Larbi *Comparative study of a sensing platform via functionalized Calix[4]resorcinarene ionophores on QCM resonator as sensing materials for detection of heavy metal ions in aqueous environments. Electroanalysis* 33 pp. 336-346., 11 p. (2021).  
(Citations:1, IF: 3.223, Q2)

### Under preparation

[PR-7] L. Eddaif and A. Shaban. *In situ QCM-I study on the applications of macrocyclic resorcinarene tetramers in chemically modified sensors platforms used to detect heavy metals ions in aqueous media.*

[PR-8] L. Eddaif and A. Shaban. *Simultaneous detection of Cd<sup>2+</sup>, Cu<sup>2+</sup>, Hg<sup>2+</sup>, and Pb<sup>2+</sup> in water based on resorcinarene electrochemical sensors.*

[PR-9] L. Eddaif and A. Shaban. *Nanostructured, Biological and Macrocyclic Sensing Platforms Applied to Monitoring Heavy Metals Ions in Water Sources: A Review.*

### Book chapters

[CH-1] L. Eddaif and A. Shaban. (2021). *Fundamentals of Sensor Technology, In Advances in Sensing Technology- Fundamental Aspects*, Z. Altintas and A. Barhoum (edits), Elsevier, Electronic ISBN: 9780323884327. **Accepted.**

[CH-2] A. Shaban, L. Eddaif, and J. Telegdi. *Sensors as useful tools for water and wastewater monitoring, In: Advances in Sensing Technology- Environmental applications.* (2021). Z. Altintas and A. Barhoum (edits), Elsevier, Electronic ISBN: 978-0-323-90223-6. **Accepted.**

## Extended Abstracts in Conference proceedings

[CR-1] L. Eddaif and A. Shaban. *Calix[4]resorcinarene Ionophores: A Heavy Metals Ions Detection Application*. *Proceedings of the 7<sup>th</sup> International Joint Conference on Environmental and Light Industry Technologies* (2019), 315-321;

[CR-2] L. Eddaif, A. Shaban, and J. Telegdi. *Application of Calixresorcinarenes as Chemical Sensors*. *Proceedings of the 1st Coatings and Interfaces Web Conference (CIWC 2019)* 1 (2019), 1-10.

[CR-3] L. Eddaif, A. Shaban, and J. Telegdi. *Calix[4]resorcinarene and Calix[4]arene Macrocycles: An Application for Heavy Metal Ions Detection in Aqueous Solutions*, *Matrafured International Meeting on Chemical Sensors* (2019).

## Oral presentations

[OP-1] L. Eddaif and A. Shaban. *Calix[4]resorcinarene Ionophores: A Heavy Metals Ions Detection Application*. *The 7<sup>th</sup> International Joint Conference on Environmental and Light Industry Technologies*, Budapest, Hungary 2019;

[OP-2] L. Eddaif, A. Shaban, and J. Telegdi. *Calix[4]resorcinarene and Calix[4]arene Ionophores: A Heavy Metals Ions Detection Application*. *TTK AKI Seminar*, RCNS, Budapest, Hungary 2019;

[OP-3] L. Eddaif, A. Shaban, and J. Telegdi. *Application of Calixresorcinarenes as Chemical Sensors*. *The 1st Coatings and Interfaces Web Conference (CIWC 2019)*, Florence, Italy 2019.

## The scientific impact of the Ph.D. work

The publications and citations metrics related to the Ph.D. work are recapitulated in the following Table:

Ph.D. work-related publications	<b>8</b>
Ph.D. work-related cumulative impact factor	<b>21.583</b>
Ph.D. work-related citations	<b>51</b> (2021.11.19)

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